Chemistry of Opium Alkaloids, 45[+]
Improvements in the Total Synthesis of Morphine

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Dedicated to Professor H. C. Beyerman on the occasion of his 80th birthday

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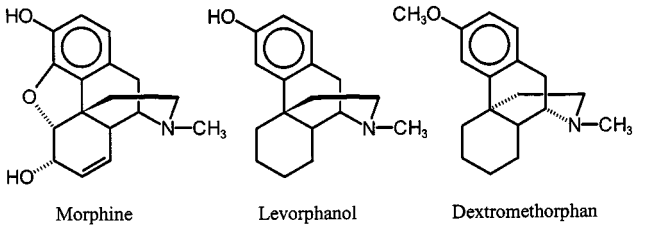
The chiral 1,2,3,4-tetrahydroisoquinoline intermediates in the Rice and Beyerman routes to morphine, (+)-(*R*)-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and (+)-(*R*)-1-(3,5-dibenzyloxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**5**), were prepared in high *ee* by ruthenium-catalyzed asymmetric transfer hydrogenation of the corresponding imine precursors (Noyori method). The yield of the key raw material in the Beyerman route, 3,5-dibenzyloxy-4-methoxyphenylacetic acid (**1**), starting from gallic acid methyl ester (**7**) was improved by a factor of 5 over previously described syntheses. Key steps in the new procedure are the selective formation of methyl 3,5-dihydroxy-4-methoxybenzoate (**9**) via the 3,5-diacetate and an improved benzylation of the hydroxyl groups in **9**.

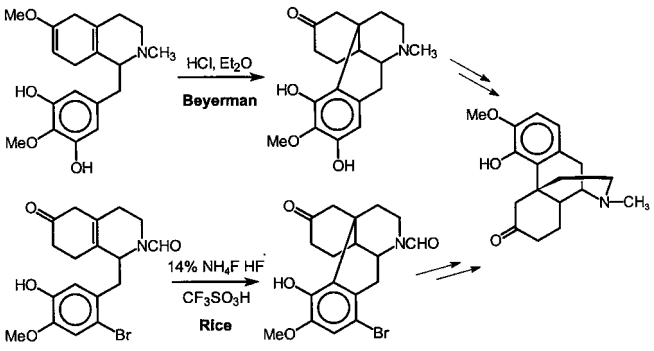
Introduction

Morphinans, exemplified by the natural product (−)-morphine and the synthetic molecules (−)-levorphanol and (+)-dextromethorphan (Scheme 1) are important analgesics and/or antitussive drugs.[1] Since Gulland and Robinson proposed the correct structure of morphine,[2] the synthesis of morphinans has attracted the attention of many synthetic chemists. The first total synthesis of morphine was published by Gates and Tschudi.[3] Subsequently, many other synthetic routes were developed.[4] The first synthesis which gave the morphine precursor (−)-dihydrothebainone in an acceptable yield was developed by Beyerman and co-workers.[5] Starting from 3,5-dibenzyloxy-4-methoxyphenylacetic acid, (−)-dihydrothebainone was obtained in 14% overall yield in 7 steps. Some years later, Rice reported an improved synthesis by a similar strategy which started from readily available compounds.[6] One of the key steps in both the Beyerman and Rice routes is the Grewe cyclization[7] of a 1-benzylisoquinoline to the morphinan structure (Scheme 2).

In both routes, optically pure (−)-dihydrothebainone is obtained by a resolution step which is inherently inefficient (maximum yield 50%). Hence, replacement by an appropriate catalytic asymmetric synthesis would constitute a significant improvement. Enantiomerically pure 1-benzylisoquinolines are key target molecules, since they can be converted into morphinans with three stereogenic centers with the correct orientation by the Grewe cyclization. Various



Scheme 1. Three important morphinan drugs



Scheme 2. The Grewe cyclization in the synthetic routes to morphine according to both Beyerman and Rice

methods for the asymmetric synthesis of 1-benzylisoquinolines have been reported.[8] The most efficient methods involve the reduction of enamides[9] or cyclic imines. Among the investigated imines were 3,4-dihydroisoquinolines or 3,4,5,6,7,8-hexahydroisoquinolines.[10] Two catalytic methods proved to be acceptably efficient for 1-benzyl-substituted imines. Noyori and co-workers employed a chiral ruthenium(II) complex prepared from an η^6-arene Ru^{II} chloride dimer and a monosulfonated 1,2-diamine in the trans-

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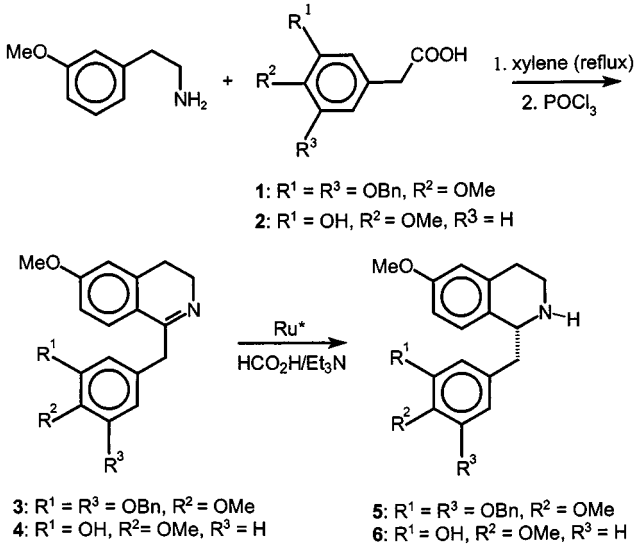
fer hydrogenation of various imines.[10g] Several 1-benzyl-3,4-dihydroisoquinolines were hydrogenated with 90−97% *ee*. The chiral iridium complex [Ir(COD)(ferrocenyldiphosphane)]BF_4 gave the octahydroisoquinoline intermediate for dextromethorphan in 89% *ee* by asymmetric hydrogenation of the corresponding imine.[10f]

In the course of our ongoing studies of morphinan syntheses[11] we have investigated possible improvements in the Beyerman and Rice syntheses. The starting material for the Beyerman route, 3,5-dibenzyloxy-4-methoxyphenylacetic acid, was synthesized in low yield.[5] Therefore, we initially investigated an alternative synthesis of this phenylacetic acid derivative. Subsequently, we investigated the catalytic asymmetric reduction of the intermediate cyclic imines in the routes of both Beyerman and Rice (Scheme 3). Since the transfer hydrogenation method of Noyori combined good performance with operational simplicity and an easy preparation of the catalyst, we investigated this procedure. We report three principal improvements leading to efficient synthetic pathways.



Scheme 3. Synthesis of the tetrahydroisoquinolines in the synthetic routes to morphine according to both Beyerman and Rice

Results and Discussion

Synthesis of 3,5-Dibenzyloxy-4-methoxyphenylacetic Acid

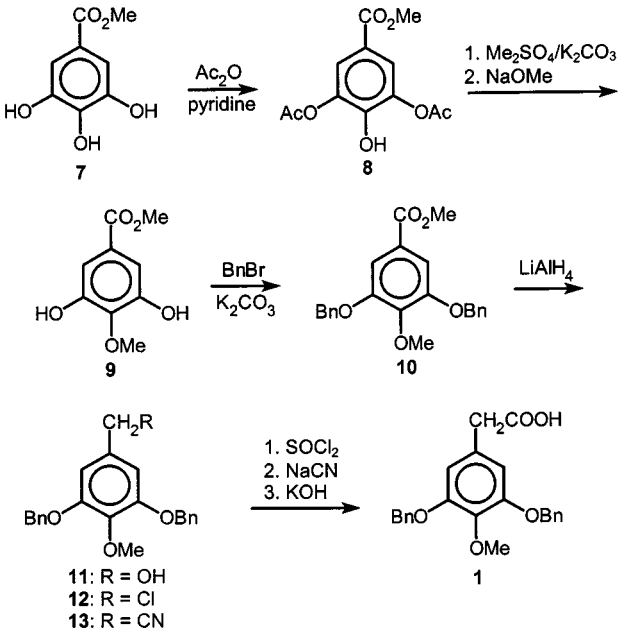
The first synthesis of 3,5-dibenzyloxy-4-methoxyphenylacetic acid (**1**) was reported by Schöpf and Winterhalder.[12] The bottleneck of this route was the methylation of methyl gallate at the 4-position, which proceeded in only 25% yield. DeGraw and co-workers[13] developed an alternative route to **1** and a similar synthesis was reported by Beyerman and co-workers.[5] Both the methods of DeGraw and Beyerman employ Schöpf's preparation of methyl 3,5-dibenzyloxy-4-methoxybenzoate. The compound was synthesized by a direct methylation of methyl gallate, which gave an isomeric mixture of methyl compounds from which the 4-methoxy compound had to be isolated. As a consequence, the overall yield of 3,5-dibenzyloxy-4-methoxyphenylacetic acid based on gallic acid was only 8% in the procedure of DeGraw and 7% as reported by Beyerman. A more sophisticated method to introduce the methoxy group at the 4-position is the selective introduction of protective groups at the 3- and 5-positions in methyl gallate. Such a methodology has been reported earlier[14] and was carried out by blocking the 3- and 5-hydroxyl groups by acetylation. We optimized this indirect methylation procedure to prepare 3,5-dibenzyloxy-4-methoxybenzoate and converted this compound into **1**.

Our route starts from methyl gallate (**7**, Scheme 4) which was acetylated with a 25% excess of acetic anhydride in pyridine according to the literature.[14] However, in our hands the 3,5-diacetate was contaminated with triacetate. Methylation of this crude diacetate with dimethyl sulfate and hydrolysis of the acetyl groups gave crude methyl 3,5-dihydroxy-4-methoxybenzoate in 48% yield and about 70% purity. When the reaction was performed with a stoichiometric amount of acetic anhydride a selective formation of the 3,5-diacetate was observed. Now the acetylation, methylation, and methanolysis could be carried out without purification of the intermediates and methyl 3,5-dihydroxy-4-methoxybenzoate (**9**) was obtained in 74% yield. It was observed that the outcome of the methylation of methyl 3,5-diacetoxy-4-hydroxybenzoate (**8**) with dimethyl sulfate was critically dependent on the purity of the starting compound.

The next step was the protection of the hydroxyl groups as benzyl ethers. Schöpf reported a yield of 52% when the reaction was performed with benzyl chloride in methanol. We performed the reaction with benzyl bromide in 2-butanone and obtained pure dibenzyloxy compound **10** in 81% yield. The next steps were performed in accordance with the procedures reported by Beyerman and co-workers.[5] The ester **10** was reduced to the benzyl alcohol **11**. Chlorination with $SOCl_2$ gave benzyl chloride **12** that was converted with NaCN into the phenylacetonitrile **13**. The nitrile was hydrolyzed to the desired phenyl acetic acid **1**. When the reported yields of the final steps are taken into account the overall yield of compound **1** based on gallic acid methyl ester can be as high as 38%. This constitutes an improvement by a factor of 5 over the previously reported procedures (see above).

Asymmetric Transfer Hydrogenation of 1-Benzyl-3,4-dihydroisoquinolines

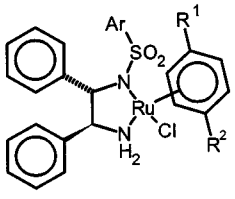
The cyclic imines were prepared according to known procedures.[5][15] The "Rice intermediate", 1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (**4**, Scheme 3) was prepared in two steps. 3-Hydroxy-4-methoxyphenylacetic acid (**2**) was treated with 3-methoxyphenylethylamine to give the amide,[15] which was then converted into **4** by a Bischler-Napieralski reaction with the aid of $POCl_3$. The "Beyerman imine", 1-(3,5-dibenzyloxy-4-meth-



Scheme 4. New synthesis of 3,5-dibenzyloxy-4-methoxyphenylacetic acid (**1**)

oxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (**3**, Scheme 3), was prepared in the same way as imine **4**, from phenylacetic acid derivative **1** and 3-methoxyphenylethylamine.[5] Imine **3** proved to be unstable and the crude imine had to be reduced immediately after its preparation.

The chiral Ru^{II} complexes (Scheme 5) were prepared from η^6-arene-Ru^{II} chloride dimeric complexes and *N*-sulfonated 1,2-diphenylethylenediamines.[10g] The monosulfonated diamines **14**−**17** were prepared by reaction of the appropriate sulfonyl chloride and (−)-(1*S*,2*S*)-1,2-diphenylethylenediamine. In all cases the formation of a small amount of disulfonated compound was observed. The monosulfonated diamines were either isolated or used without purification. The ruthenium complexes were formed by reaction of the monosulfonated diamine with the dimer of η^6-*p*-cymene-Ru^{II} chloride or the dimer of η^6-benzene-Ru^{II} chloride in the presence of triethylamine as previously described by Noyori and co-workers.[10g] The complexes **18**, **19**, and **20** were isolated and purified by crystallization, whereas **21** and **22** were used after in situ preparation.



18: Ar = 4-$CH_3C_6H_4$, R^1 = CH_3, R^2 = $CH(CH_3)_2$
19: Ar = 4-$CH_3C_6H_4$, R^1 = R^2 = H
20: Ar = 2,4,6-$(CH_3)_3C_6H_2$, R^1= CH_3, R^2 = $CH(CH_3)_2$
21: Ar = 1-naphthyl, R^1 = CH_3, R^2 = $CH(CH_3)_2$
22: Ar = 2,4,6-$(CH(CH_3)_2)_3C_6H_2$, R^1 = CH_3, R^2 = $CH(CH_3)_2$

Scheme 5. Structure of the applied chiral ruthenium complexes

First, we investigated the asymmetric transfer hydrogenation of the "Rice imine" **4** (Scheme 3). We found that the reactions were best carried out in dimethylformamide at 20−30°C. When the reactions were performed in acetonitrile or dichloromethane, we observed deactivation of the catalyst. Deactivation was also observed when the reactions were carried out at temperatures higher than 30°C. Preliminary experiments showed that complex **20** was the best catalyst for the transfer hydrogenation of **4**. Tetrahydroisoquinoline **6** was formed with excellent *ee* (99%) and the amine could be isolated in 73% yield by crystallization.

The synthesis of **5**, the intermediate in the Beyerman synthesis of morphine, was performed under the same conditions applied for amine **6**. Some representative results obtained with the complexes **18**−**22**, in the presence of a 5:2 formic acid-triethylamine azeotropic mixture as hydrogen donor, are summarized in Table 1.

Table 1. Results of the asymmetric transfer hydrogenation of imine **3** catalyzed by chiral ruthenium complexes.[a]

Entry	Catalyst	mol-% cat.	*t*/h[b]	% *ee*[c]
1	18	5	2	86
2	18[d]	5	2	84
3	19	5	2	81
4	20	5	1.5	81
5	21[d]	10	4	67
6	22[d]	10	2	62

[a] The reactions were carried out in DMF at 20°C. − [b] Time taken for complete conversion of the imine as shown by TLC. − [c] Determined by HPLC analysis of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) derivative.[9] − [d] The complex was prepared in situ.

The best results were obtained with [(+)-(1*S*,2*S*)-*N*-tosyl-1,2-diphenylethylenediamine-η^6-cymene]ruthenium(II) chloride (**18**). Complexes **21** and **22** with a bulkier ligand gave compound **5** with the lowest *ee* values (Entries 5 and 6). This was not due to the fact that these catalysts were prepared in situ, since the transfer hydrogenation reaction with **18** prepared in situ gave **5** with only a slightly lower *ee* than that observed with an isolated complex (Entries 1 and 2). In all reactions, a relatively apolar by-product, probably an *N*-formylisoquinoline formed by reaction of **5** with formic acid, was present in small amounts according to TLC. Tetrahydroisoquinoline **5** was formed in 75−80% yield. Isolation of the compound proved to be difficult. Crystallization as the hydrobromide[5] was cumbersome and column chromatography over silica gel gave pure **5** in only 23% yield. However, it might be possible to use the crude compound in the next step of the Beyerman route, Birch reduction to the hexahydroisoquinoline.

In conclusion, we improved the yield of 3,5-dibenzyloxy-4-methoxyphenylacetic acid by a factor of 5. In addition, we investigated the ruthenium-catalyzed asymmetric transfer hydrogenation of cyclic imines in the synthesis of 1,2,3,4-tetrahydroisoquinoline intermediates in two synthetic routes to morphine. The method works particularly well for the Rice intermediate (+)-(*R*)-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, which

was formed with 99% *ee* and could be isolated in 73% yield. The other morphine precursor, the Beyerman intermediate (+)-(*R*)-1-(3,5-dibenzyloxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, was prepared with 86% *ee*. Since the isolation of the intermediates in the Beyerman route proved to be cumbersome, the Rice route seems to be more favourable for the transfer hydrogenation approach.

Experimental Section

General: Mass spectra were determined using a VG70-SE spectrometer. − ^{1}H and ^{13}C NMR spectra were recorded with a Varian T-60 spectrometer or a Varian INOVA 300 spectrometer. Unless otherwise stated $CDCl_3$ was used as solvent and tetramethylsilane as reference. − Optical rotations were measured on a Perkin −Elmer 241 polarimeter at the sodium D line (λ = 589 nm). − Melting points are uncorrected. − Column chromatogaphy was performed on silica gel (Merck kieselgel 60, particle size 63−200 μm) and thin layer chromatography (TLC) on deactivated silica (0.25 mm, Merck F_{254}). − Analytical HPLC was performed using a Waters M-6000A pump on a reversed-phase column (Nucleosil C_{18} or Novopak C_{18}) using a mixture of acetonitrile and water (60/40) as eluent, with detection on a Shimadzu SPD-6A UV spectrophotometric detector. − Methyl gallate, 3-methoxyphenylethylamine, (−)-(1*S*,2*S*)-1,2-diphenylethylenediamine, 2,4,6-triisopropylbenzenesulfonyl chloride, naphthalene-1-sulfonyl chloride, and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) were purchased from Fluka. 2-Mesitylenesulfonyl chloride was purchased from Acros. $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and $[RuCl_2(\eta^6\text{-benzene})]_2$ were purchased from Aldrich. 3-Hydroxy-4-methoxyphenylacetic acid (**2**) was prepared according to a known procedure.[15]

Methyl 3,5-Dihydroxy-4-methoxybenzoate (9): Acetic anhydride (135 g, 1.33 mol) was added dropwise over 2.5 h to a solution of methyl gallate (122 g, 0.663 mol) in 200 mL of pyridine. The viscous solution was stirred overnight at room temperature. After evaporation of the pyridine a solid product was obtained. Recrystallization from 160 mL of toluene gave methyl 3,5-diacetoxy-4-hydroxybenzoate (**8**, 158.4 g, 0.591 mol, 89%) as a white solid . The compound was suspended in 300 mL of acetone and potassium carbonate (100 g, 0.724 mol) and dimethyl sulfate (93.5 g, 0.742 mol) were added. The mixture was heated at reflux until TLC showed a complete conversion of the starting compound and filtered. The filtrate was evaporated under reduced pressure to give a white solid. The precipitate was suspended in 400 mL of water and extracted with chloroform (2 × 100 mL). Evaporation of the solvent also gave a white solid. The combined solid portions were dissolved in 300 mL of methanol. A solution of sodium methoxide in methanol (13 g, 0.25 mol) was added and the mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure and the residue was added to dilute sulfuric acid (0.5 m, 300 mL). The mixture was extracted with diethyl ether (2 × 200 mL, 2 × 100 mL). The combined ether layers were washed with water, a saturated solution of $NaHCO_3$ (200 mL), and a saturated solution of NaCl (200 mL). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to give methyl 3,5-dihydroxy-4-methoxybenzoate (**9**, 97.4 g, 0.492 mol, 74% based on methyl gallate) as a white solid. − M.p. 136−140 °C (ref.[12]: 136 °C). − ^{1}H NMR ([D$_6$]DMSO): δ = 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.95 (s, 2 H, aromatic protons), 9.60 (br. s, 2 H, 2 × OH). − ^{13}C NMR: δ = 165.95, 150.63, 139.66, 124.36, 108.45, 59.58, 51.80.

Methyl 3,5-Dibenzyloxy-4-methoxybenzoate (10): Methyl 3,5-dihydroxy-4-methoxybenzoate (**9**, 50 g, 0.253 mol) and anhydrous potassium carbonate (77 g, 0.558 mol) were suspended in 250 mL of 2-butanone. The mixture was mechanically stirred and heated at reflux. Benzyl bromide (95 g, 0.555 mol) was added dropwise over 1.5 h. The mixture was stirred for another 1 h, and after cooling, was diluted with 600 mL of water. The suspension was extracted with chloroform (3 × 300 mL). The combined chloroform layers were washed with water (400 mL), a saturated solution of $NaHCO_3$ (400 mL), and a saturated solution of NaCl (400 mL). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure. The residue was crystallized from ethanol (100 mL). After filtration and washing with ethanol (250 mL) methyl 3,5-dibenzyloxy-4-methoxybenzoate (**10**, 77.0 g, 0.204 mol, 81%) was obtained as a white solid. − M.p. 117−119 °C (ref.[12]: 121−122 °C, ref.[5b]: 120−121 °C). − ^{1}H NMR: δ = 3.87 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 5.15 (s, 4 H, benzylic protons), 7.40 (m_c, 12 H, aromatic protons). − ^{13}C NMR: δ = 166.42, 152.12, 143.60, 136.59, 128.46, 127.90, 127.31, 124.89, 109.23, 71.16, 60.93, 52.13.

3,5-Dibenzyloxy-4-methoxybenzyl Alcohol (11): Methyl 3,5-dibenzyloxy-4-methoxybenzoate (**10**, 75.6 g, 0.200 mol) was suspended in 300 mL of warm THF and added dropwise to a suspension of lithium aluminium hydride (7.6 g, 0.200 mol) in 100 mL of THF. After 1 h of stirring, water (7 mL), a solution of sodium hydroxide (15%, 7 mL), and again water (20 mL) were added. After filtration, the solid residue was washed with warm THF (100 mL) and heated twice at reflux in THF, followed by filtration of the warm solution. The combined THF extracts were evaporated under reduced pressure. This gave 3,5-dibenzyloxy-4-methoxybenzyl alcohol (**11**, 68.3 g, 0.195 mol, 98%) as an oil that crystallized after the addition of some pure crystals. − M.p. 102−105 °C (ref.[5b]: 105−106 °C). − ^{1}H NMR: δ = 3.88 (s, 3 H, OCH_3), 4.52 (s, 2 H, CH_2OH), 5.12 (s, 4 H, benzylic protons), 6.63 (s, 2 H, aromatic protons), 7.40 (m_c, 10 H, aromatic protons). − ^{13}C NMR: δ = 152.70, 138.80, 137.15, 136.48, 128.53, 127.86, 127.25, 106.52, 71.11, 65.33, 60.95.

3,5-Dibenzyloxy-4-methoxybenzyl Chloride (12): Thionyl chloride (6.2 g, 0.052 mol) was added dropwise to a solution of 3,5-dibenzyloxy-4-methoxybenzyl alcohol (**11**, 10.5 g, 0.030 mol) in 80 mL of benzene. The mixture was stirred for 1 h at room temperature and then heated at reflux for 1 h. The solvent and the excess of thionyl chloride were evaporated under reduced pressure. Ethanol (25 mL) was added to the residue. After cooling, the suspension was filtered and washed with ethanol. This gave 3,5-dibenzyloxy-4-methoxybenzyl chloride (**12**, 9.92 g, 0.027 mol, 90%) as a white solid. − M.p. 78−80 °C (ref.[5b] 77−78 °C). − ^{1}H NMR: δ = 3.88 (s, 3 H, OCH_3), 4.45 (s, 2 H, CH_2Cl), 5.12 (s, 4 H, benzylic protons), 6.66 (s, 2 H, aromatic protons), 7.40 (m_c, 10 H, aromatic protons). − ^{13}C NMR: δ = 152.54, 139.56, 136.82, 132.58, 128.44, 127.81, 127.19, 108.32, 71.16, 60.87, 46.58.

3,5-Dibenzyloxy-4-methoxybenzyl Cyanide (13): 3,5-Dibenzyloxy-4-methoxybenzyl chloride (**12**, 19.50 g, 0.053 mol) and sodium cyanide (3.96 g, 0.080 mol) were dissolved in 60 mL of DMSO. After 21 h of stirring at room temperature, 530 mL of water was added dropwise. The beige precipitate was filtered, dried, and dissolved in benzene. Water was evaporated azeotropically and the residue was dissolved in 25 mL of warm benzene. Hexane (75 mL) was added cautiously to the warm solution. The suspension was filtered and washed with hexane to yield 3,5-dibenzyloxy-4-methoxybenzyl cyanide (**13**, 16.79 g, 0.046 mol, 87%) as a beige solid, melting at 79−81 °C. It was recrystallized from ethanol to give 14.96 g (0.041 mol, 77%) of **13** as a white solid. − M.p. 92−94 °C (ref.[5b]:

92−93.5 °C, ref.[13]: 92−93.5°C). − ^{1}H NMR: δ = 3.60 (s, 2 H, CH_2CN), 3.88 (s, 3 H, OCH_3), 5.12 (s, 4 H, benzylic protons), 6.57 (s, 2 H, aromatic protons), 7.40 (m_c, 10 H, aromatic protons). − ^{13}C NMR: δ = 152.87, 139.21, 136.63, 128.50, 127.91, 127.20, 124.98, 117.64, 107.68, 71.22, 60.93, 23.66.

3,5-Dibenzyloxy-4-methoxyphenylacetic Acid (1): 3,5-Dibenzyloxy-4-methoxybenzyl cyanide (**13**, 11.82 g, 0.0328 mol) and potassium hydroxide (17 g, 0.25 mol) were dissolved in a mixture of water (50 mL) and 2-methoxyethanol (60 mL). The mixture was heated at reflux for 2 h. After cooling, the solution was poured onto 600 mL of water and the mixture was extracted with ether (100 mL). The aqueous layer was acidified (pH 2) with a solution of hydrochloric acid (6 m, 60 mL). The suspension was extracted with chloroform (3 × 100 mL) and the combined organic layers were washed with a saturated solution of NaCl (300 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, a yellow solid was obtained. Recrystallization from ethanol gave **1** (8.91 g, 0.0235 mol, 72%) as a white solid. − M.p. 134−135 °C (ref.[5b]: 138−141°C, ref.[12]: 138−139 °C, ref.[13]: 138−140 °C). − ^{1}H NMR: δ = 3.51 (s, 2 H, CH_2COOH), 3.87 (s, 3 H, OCH_3), 5.11 (s, 4 H, benzylic protons), 6.57 (s, 2 H, aromatic protons), 7.40 (m_c, 10 H, aromatic protons). − ^{13}C NMR: δ = 177.04, 152.64, 138.93, 137.04, 128.52, 127.88, 127.35, 109.28, 71.32, 60.93, 41.08.

1-(3,5-Dibenzyloxy-4-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (3): A mixture of 3,5-dibenzyloxy-4-methoxyphenylacetic acid (**1**, 4.54 g, 12.0 mmol) and 3-methoxyphenylethylamine (1.83 g, 12.1 mmol) was heated at reflux in *p*-xylene (40 mL) for 6 h for removal of water. Cyclohexane (40 mL) was added to the solution and a white precipitate was formed. The suspension was filtered and washed with cyclohexane (50 mL). This gave *N*-(3-methoxyphenylethyl)-(3,5-dibenzyloxy-4-methoxyphenyl)acetamide (4.89 g, 9.60 mmol, 80%) as a slightly beige powder. − M.p. 76−78 °C (ref.[5b]: 81−82 °C). − ^{1}H NMR: δ = 2.63 (t, 2 H, $CH_2$$CH_2$N), 3.38 (s, 2 H, CH_2CO), 3.40 (t, 2 H, $CH_2$$CH_2$N), 3.72 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.07 (s, 4 H, benzylic protons), 5.35 (m_c, 1 H, NH), 6.42 (s, 2 H, aromatic protons), 6.60 (m_c, 3 H, aromatic protons), 7.15 (t, 1 H, aromatic proton, 7.40 (m_c, 10 H, aromatic protons of benzyloxy groups). − ^{13}C NMR: δ = 170.67, 159.82, 152.82, 140.24, 138.74, 136.96, 130.03, 129.52, 128.55, 127.91, 127.24, 120.96, 114.74, 111.66, 109.03, 71.01, 60.91, 55.12, 44.03, 40.50, 35.40. − The acetamide (0.100 g, 0.196 mmol) was dissolved in benzene (5 mL) and $POCl_3$ (0.06 mL, 0.64 mmol) was added. The mixture was heated at reflux for 1 h and then poured onto ice-water (25 mL). Dichloromethane and a solution of sodium hydroxide (33%, 1 mL) were added. The mixture was stirred for 15 min. After separation the aqueous layer was extracted with chloroform (2 × 25 mL). The combined organic layers were washed with water (25 mL), a saturated solution of NaCl (25 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, imine **3** (0.0884 g, 0.179 mmol, 91%) was obtained as a TLC-pure, brown oil. The compound was unstable. − ^{1}H NMR: δ = 2.60 (t, 2 H), 3.67 (t, 2 H), 3.82 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.95 (m_c, 2 H), 5.10 (s, 4 H, benzylic protons), 6.56 (s, 2 H, aromatic protons), 6.65 (m_c, 2 H, aromatic protons), 7.34 (m_c, 11 H, aromatic protons). − ^{13}C NMR: δ = 152.46, 140.32, 138.05, 128.44, 127.98, 127.69, 127.41, 127.31, 127.20, 113.09, 112.06, 108.39, 70.95, 60.87, 55.38, 45.74, 42.13, 26.15.

1-(3-Hydroxy-4-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (4): 3-Hydroxy-4-methoxyphenylacetic acid (**2**, 1.00 g, 5.49 mmol) and 3-methoxyphenylethylamine (0.80 mL, 0.83 g, 5.50 mmol) were heated at reflux in *p*-xylene (20 mL) for 4 h. *p*-Xylene was removed under reduced pressure. The residue was diluted with chloroform (100 mL) and washed with diluted hydrochloric acid (0.5 m, 50 mL), a saturated solution of $NaHCO_3$ (100 mL), and a saturated solution of NaCl (100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was dissolved in acetonitrile (10 mL) and $POCl_3$ (1 mL, 1.70 g, 11 mmol) was added. The mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was heated at reflux in water (25 mL) for 1 h. Chloroform (20 mL) was added and the mixture was rendered alkaline with dilute ammonia. After separation, the aqueous layer was extracted with chloroform (25 mL). The combined organic layers were washed with a saturated solution of NaCl (25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a brown foam. Imine **4** (0.427 g, 1.44 mmol, 26%) was crystallized from methanol and obtained as a beige solid. − M.p. 153−156 °C (ref.[15]: 155 °C). − ^{1}H NMR (60 MHz, [D$_6$]DMSO): δ = 2.6 (t, 2 H, CH_2), 3.7 (m_c, 2 H, CH_2), 3.8 (s, 3 H, OCH_3), 3.9 (s, 2 H, CH_2), 6.7 (m_c, 4 H, aromatic protons), 7.4 (m_c, 2 H, aromatic protons).

Synthesis of Monosulfonated (1*S*,2*S*)-1,2-Diphenylethylenediamines

(−)-(1*S*,2*S*)-*N*-Tosyl-1,2-diphenylethylenediamine [(*S*,*S*)-TsDPEN, 14]: (−)-(1*S*,2*S*)-1,2-Diphenylethylenediamine (0.246 g, 1.16 mmol) was added to a solution of *p*-toluenesulfonyl chloride (0.221 g, 1.16 mmol) and triethylamine (0.30 mL, 2.10 mmol) in dichloromethane (10 mL). After stirring for 50 min at room temperature, the solution was diluted with dichloromethane (20 mL) and washed with a solution of sodium hydroxide (0.5 m, 10 mL), a saturated solution of NaCl (10 mL), and then dried (Na_2SO_4). After removal of the dichloromethane under reduced pressure, the residue was diluted with benzene and evaporated again to remove triethylamine azeotropically. This procedure was repeated twice. The oily residue was crystallized from a mixture of benzene (2 mL) and hexane (2 mL). This gave the monotosylate (0.206 g, 0.56 mmol, 49%) as a white powder. − M.p. 125−126 °C. − $[\alpha]^{24}$ = −89 (*c* = 0.98 in methanol). − ^{1}H NMR: δ = 2.30 (s, 3 H, CH_3), 2.50 (br. s, 2 H, NH_2), 4.20 [d, 1 H, CH, *J* = 5.5 Hz], 4.42 [d, 1 H, CH, *J* = 5.5 Hz], 6.96 (d, 2 H, aromatic protons of tosyl group), 7.12 (m_c, 10 H, aromatic protons), 7.34 (d, 2 H, aromatic protons of tosyl group). − ^{13}C NMR: δ = 142.47, 140.87, 138.98, 137.19, 129.08, 128.43, 128.20, 127.55, 127.35, 127.09, 126.87, 126.68, 63.11, 60.45, 21.40.

(−)-(1*S*,2*S*)-*N*-(2-Mesitylenesulfonyl)-1,2-diphenylethylenediamine [(*S*,*S*)-MesDPEN, 15]: This monosulfonate was prepared according to the procedure described for compound **14**. 2-Mesitylenesulfonyl chloride (0.222 g, 1.02 mmol) and (−)-(1*S*,2*S*)-diphenylethylenediamine (0.212 g, 1.00 mmol) gave 0.302 g (0.77 mmol, 77%) of **15** as a yellow oil. TLC showed the presence of traces of ditosylate. − $[\alpha]^{20}$ = −58 (*c* = 0.81 in methanol). − ^{1}H NMR: δ = 1.70 (br. s, 2 H, NH_2), 2.20 (s, 3 H, CH_3), 2.39 (s, 6 H, 2 × CH_3), 3.99 [d, 1 H, CH, *J* = 6.8 Hz], 4.31 [d, 1 H, CH, *J* = 7.0 Hz], 6.18 (br. s, 1 H, NH), 7.00 (m_c, 12 H, aromatic protons). − ^{13}C NMR: δ = 141.71, 141.56, 138.75, 138.62, 131.52, 128.34, 127.84, 127.40, 127.26, 127.15, 126.48, 63.65, 60.81, 22.88, 22.72, 20.79.

(−)-(1*S*,2*S*)-*N*-(2,4,6-Triisopropylbenzenesulfonyl)-1,2-diphenylethylenediamine (16): This monosulfonate was prepared according to the procedure described for compound **14**. (−)-(1*S*,2*S*)-1,2-Diphenylethylenediamine (0.246 g, 1.16 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (0.351 g, 1.16 mmol) gave 0.440 g (0.92 mmol, 79%) of **16** as a TLC-pure yellow oil which solidified on standing. − M.p. 45−47°C − $[\alpha]^{20}$ = −57 (*c* = 0.49, CH_3OH). − ^{1}H NMR: δ = 1.08 (d, 6 H, 2 × CH_3 of isopropyl group), 1.17 (d, 6 H, 2 × CH_3 of isopropyl group), 1.21 (d, 6 H, 2 × CH_3 of

isopropyl group), 1.65 (br. s, 2 H, NH_2), 2.82 (sept., 1 H, CH of isopropyl group), 3.95 (sept., 2 H, 2 × CH of isopropyl group), 3.95 (d, 1 H, CH), 4.48 [d, 1 H, CH, J = 7.7 Hz], 6.12 (br. s, 1 H, NH), 6.82 (m_c, 2 H, aromatic protons), 6.98 (m_c, 2 H, aromatic protons), 7.16 (m_c, 3 H, aromatic protons). − ^{13}C NMR: (δ = 152.31, 149.66, 141.92, 138.65, 133.95, 128.36, 127.82, 127.50, 127.31, 127.27, 126.81, 123.26, 63.50, 61.21, 34.12, 29.79, 24.89, 24.73, 23.66, 23.63. − MS: 478 (M^+, 0.1), 267 (18), 187 (24), 145 (42), 106 (100), 93 (39), 77 (33).

(−)-(1*S*,2*S*)-*N*-(Naphthalene-1-sulfonyl)-1,2-diphenylethylenediamine (17): This monosulfonate was prepared according to the procedure described for compound **14**. The oily residue was crystallized from a mixture of benzene and cyclohexane. Thus, (−)-(1*S*,2*S*)-1,2-diphenylethylideneamine (0.200 g, 0.943 mmol) and naphthalene-1-sulfonyl chloride (0.214 g, 0.944 mmol) gave 0.213 g (0.530 mmol, 56%) of **17** as a white powder. − M.p. 48−50 °C − $[\alpha]^{20}$ = −257 (c = 1.20, CH_3OH). − ^{1}H NMR: (δ = 1.65 (br. s, 2 H, NH_2), 4.00 (d, 1 H, CH), 4.40 (d, 1 H, CH), 6.45 (m_c, 1 H, NH), 6.92 (m_c, 10 H, aromatic protons), 7.20 (m_c, 2 H, aromatic protons), 7.56 (m_c, 2 H, aromatic protons), 7.79 (m_c, 3 H, aromatic protons). ^{13}C NMR: (δ = 141.27, 138.59, 135.06, 134.06, 133.65, 129.26, 128.78, 128.06, 127.88, 127.81, 127.34, 127.24, 126.96, 126.85, 126.44, 126.22, 124.77, 123.79, 63.75, 60.45.

Synthesis of the Ruthenium Catalysts: The ruthenium complexes **18−20** were prepared according to the method described by Noyori and co-workers,[10g] from the pure monosulfonated diphenylethylenediamines and [η^6-arene-$RuCl_2$]$_2$

Synthesis of (+)-(*R*)-1-(3,5-Dibenzyloxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5)

A. General Procedure with Ruthenium Complexes 18−20: 1-[(3,5-Dibenzyloxy-4-methoxy)benzyl]-6-methoxy-3,4-dihydroisoquinoline (**3**, freshly prepared crude imine) and the ruthenium complex (2.5 mol%) were dissolved in DMF. An azeotropic mixture of formic acid and triethylamine (5:2, 0.5 mL per mmol of imine) was added and the mixture was stirred at 20°C. The reaction was monitored by TLC (CH_2Cl_2/MeOH/NH_4OH = 90:10:0.5) and after complete conversion of the imine, ethyl acetate was added. The organic layer was washed with a dilute solution of hydrochloric acid (1 m), water, a saturated solution of $NaHCO_3$, and a saturated solution of NaCl. After drying (Na_2SO_4), the solvent was evaporated under reduced pressure. Typical yields of product were 75−80%. Isolation of **5** was possible by column chromatography over silica gel (eluent: ethyl acetate/MeOH/NH_4OH, 92:5:3), but the amine was obtained in low yield (23%, prepared with complex **18**).

The enantiomeric excess (see Table 1) was measured by HPLC analysis of the GITC derivative. Therefore, crude **5** was dissolved in acetonitrile and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (1.5 equivalents) was added. The mixture was stirred for 30 min at room temperature. After dilution, the reaction mixture was directly analyzed by HPLC.

B. General Procedure with Ruthenium Complexes 18, 21, and 22. − In Situ Preparation: The chiral ligand and [η^6-*p*-cymene-$RuCl_2$]$_2$ (0.5 equivalents) were dissolved in DMF and 2 equivalents of triethylamine were added. The mixture was heated for 1 h at 80°C. After cooling, crude imine **3** and an azeotropic mixture of formic acid and triethylamine (5:2) were added, and the mixture was stirred at 20 °C. On complete conversion of the imine, the mixture was worked up as described under method A. After conversion of the crude amine into the GITC derivative, the mixture was analyzed with HPLC to measure the *ee* (Table 1).

(+)-(*R*)-1-(3-Hydroxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6): 1-(3-Hydroxy-4-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (**4**, 150 mg, 0.51 mmol) and (−)-(*S*,*S*)-MesDPEN-η^6-*p*-cymene-Ru^{II}Cl (**20**, 8.6 mg, 0.013 mmol) were dissolved in DMF (1.5 mL). An azeotropic mixture of formic acid and triethylamine (5:2, 0.25 mL) was added and the mixture was stirred for 90 min at 30 °C. The mixture was diluted with ethanol (4 mL) and water (4 mL) and basified with dilute ammonia (2 m, 3 mL). A precipitate was formed which was filtered and washed with ethanol. This gave a beige powder which was heated at reflux in ethanol for 30 min. After filtration, **6** (110 mg, 0.37 mmol, 73%) was obtained as a white powder. The *ee* was 99% as was measured by HPLC of the GITC derivative. − $[\alpha]^{20}$ = +38 (c = 0.20, DMF, ref.[12]: [α] = + 38, c = 0.25 in DMF). − M.p. 214−215 °C (ref.[12]: 217.5−219 °C). − ^{1}H NMR ([D_6]DMSO + TFA): δ = 3.00 (m_c, 3 H), 3.25 [dd, 2 H, CH_2, J = 6.0 Hz, J = 14.0 Hz], 3.40 (m_c, 1 H), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.64 (m_c, 1 H, NCH), 6.72 (dd, 1 H, aromatic proton), 6.80 (m_c, 3 H, aromatic protons), 6.91 (d, 1 H, aromatic proton), 7.07 (d, 1 H, aromatic proton). − ^{13}C NMR: δ = 146.85, 146.53, 133.30, 128.12, 127.93, 124.35, 120.25, 117.27, 116.76, 113.44, 113.15, 112.93, 112.32, 55.59, 55.10, 25.12. −IR (KBr): $\tilde{\nu}$ = 3299 cm^{-1} (m), 2988 (m), 2934 (m), 2832 (m), 2601 (w), 1612 (w), 1582 (m), 1502 (s), 1468 (w), 1454 (w), 1438 (m), 1371 (m), 1309 (m), 1288 (s), 1258 (s), 1223 (s), 1176 (w), 1154 (w), 1132 (s), 1045 (m), 1034 (m), 805 (m). − HRMS: $C_{18}H_{21}NO_3$: calcd. 299.1521; found 299.1530.

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